AstraZeneca

Date: JUL 18 2002

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Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number 02D-0232
Response to FDA Call for Comments
International Conference on Harmonisation; Draft Guidance on S7B Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

Dear Sir or Madam:

Reference is made to the June 14, 2002 Federal Register notice announcing the availability of draft guidance entitled "S7B Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals".

AstraZeneca has reviewed this guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Dr. JoAnne Saye, Preclinical Sciences Director, at (610) 695-1370.

Sincerely,

Lewis B. Kinter, Ph.D.
Senior Director
AstraZeneca Pharmaceuticals L.P.

02D-0232 C1

LBK\alw

Enclosure

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Docket Number 02D-0232: Response to FDA Call for Comments
International Conference on Harmonisation; Draft Guidance on S7B
Safety Pharmacology Studies for Assessing the Potential for Delayed
Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

General Comments

- There is no clear-cut description for QT assessment with human-specific metabolites in the draft guidelines. The major human-specific metabolite should be evaluated on QT assessment. The ICHS7B guidelines should include description on when and how the major human-specific metabolites are evaluated on QT assessment.
- The guideline should give recommendation on what constitutes a "positive signal" in any of the listed assays.
- Safety margins: Could the guideline include some clearer recommendations on how to evaluate and define the safety margin for the QT liability of new drugs? Concepts of risk associated with hERG findings are discussed in a recent paper by Webster et al. (2002). The predictions that could be made today are not totally reliable but it would be useful to outline that, based on clinical experience for a reasonable large number of drugs, findings in the hERG assay can give an indication of thc probability (low, medium, high) of there being a QT liability in man and that this can be built into the screening strategy.
  A. *2.3.3 Implication of Nonclinical Studies. 'Any non-antiarrhythmic pharmaceutical that blocks .... should be considered to pose a risk to humans, especially if in vivo effects occur at concentrations that are <u>low multiples</u> of the anticipated therapeutic plasma concentrations.'*
  In the case of marked inter-subject variation in the plasma concentrations, hypokalemia, bradycardia and some of variant Iks channel genes, concentrations to be considered to pose a risk to humans are higher multiples of anticipated therapeutic plasma concentrations. The safety margin in thc ICHS7B guidelines should be discussed in the light of the risk factors such as inter-subject variation in the plasma concentrations, hypokalemia, bradycardia, variant Iks channel genes and so on.
- Selection of concentration and doses to be tested should be based on safety margins. To test compounds close to their solubility limit will probably result in most compounds carrying a hERG positive signal. In general, exposure should be demonstrated for in vivo studies in order to relate functional changes to concentration.
- The association between pharmacological class/chemical class and the risk of QT liability should be discouraged. It is becoming increasingly evident (both with in AZ and in other companies) that it is possible to manipulate the SAR so that for a given pharmacological class/chemical class, there will be drugs/compounds with hERG and QT activities whereas some will be without any activity on hERG or QT.
- Can the *in vitro* and *in vivo* test systems for QT assessment recommended by the ICHS7B guidelines be classified into two or three categories, like ICHS7A?

- For example,
  1) Supreme QT assessment tests (in vitro/in vivo tests) before human use (GLP),
  2) Follow-up QT assessment tests after the supreme QT assessment tests (GLP if feasible),
  3) Supplement QT assessment tests when there is cause of concern during clinical trials (GLP if feasible).
- The industry should be encourage to provide data on proarrhythmic models to identify if any of these models are relevant to proarrhythmic risk to humans.

Page or Line Number	**Comment or proposed replacement text**
3, 43	Include"..... influx of Na^+ through slowly inactivating sodium channels (I Na, late) and outward repolarizing..."
5, 103	Include " ..properties, global ventricular repolarization, arrhythmias and...
5, 106	The text indicates that carefully designed studies allow for evaluation of metabolites and safety margins. True safety margins are calculated from plasma exposures rather than dose. Thus, this statement uses a very indirect approach to indicate that pharmacokinetic analyses should be performed. Is PK analysis to be optional or required?
6, 141	Indicate what species are considered acceptable for determining the relative risk of QT interval prolongation in humans. Please cite section 3.1.3 for explanation why rodents are not appropriate models.
6, 146	Should it read "....assessment as part of the core battery..." ?
6, 160	Change "gender" to "gender(s)".
7,180	The abbreviations MAP and ERP are not explained see also line 289.
7,181	Section 3.4.3.1 which is cited does not exist in the document.
7, 189	These studies are indeed valuable. Are they also required?
7, 200-206	This passage need to be clearer. How is potential risk estimated from QT prolongation, how much of a margin is safe enough for the benefit of cancer patients? Heart patients? Psychiatric patients etc.?
8, 243	The sentence beginning "While more fragile..." does not appear to be a true sentence. Suggest deleting the word "while".
8, 219	Section 3.1.1 Positive control substances and reference compounds should be defined.
9, 279	In vitro assays may well be reliable for predicting safety margins, but the data package is likely not sufficient for predicting safety margins. Might the authors consider using the word sufficient?

Page or Line Number	Comment or proposed replacement text
10, 307-316	An additional factor to be included in this list should be comparative physiology of cardiac depolarization (e.g. humans and dogs vs. pigs).
11, 402	Should read "References"
12, 448	Should it read "(see section 3.4)"?
13, 469	First word in the title of the reference article is "Drugs".
14, 513	Include "...dissection trauma and to anoxia-related depolarization due to insufficient perfusion of deeper tissue levels."
14, 517	The authors note that for this in vitro assay, solvent/vehicle should be tested separately. In fact, solvent/vehicle effects should be evaluated in all in vitro systems discussed in this document. Perhaps a general statement on this issue placed in the beginning of the in vitro assay section will suffice?
14, 507	Although the heading for this section is entitled; "Action potential recordings in Purkinje fibers, papillary muscle, ventricular trabeculae", there are no references listed which provide information for the reader on either papillary muscle or ventricular trabeculae techniques and relative utility. Suggested useful references related to the papillary muscle preparation and assay is: Baskin EP, Serik CM, Wallace AA et al. Effects of new and potent methanesulfonanilide class iii antiarrhythmic agents on myocardial refractoriness and contractility in isolated cardiac muscle. J. cardiovasc. Pharmacol. 18: 406-414, 1991. Cingolani HE, Wiedman RT, Lynch JJ et al. Myocardial contractile behavior of a new sotalol derivative. J. Cardiovasc. Pharmacol. 17: 83-89, 1991.
15, 574	3.3 High Throughput In Vitro Screening Assays Yet another relatively reliable screening method is the Rb-86-based flux assay, based on the idea that potassium channels transport not only K^+ ions but also Rb^+ ions. Like patch-clamp electrophysiology the Rb-86-flux methodology is a functional K^+ assay. However, in contrast to patch-clamp studies, it only gives data on Rb-flux at a static condition, i.e. at channels depolarized by elevation of external potassium concentration. Another drawback is that IC_{50}-values generated by the method are 5-20-fold higher than corresponding values as measured with the patch-clamp technique in mammalian cells. For both these reasons, the method is not considered as a substitute for the voltage clamp assays described in the document. Reference: Tang W, Kang J, WuX, Rampe D, Vang L, Shen H, Li Z, Dunnington D, Garyantes T.: Development and evaluation of high throughput functional assay methods for hERG potassium channel. Journal of Biomolecular Screening, 6 (5); 325-331, 2001.

Page or Line Number	Comment or proposed replacement text
16, 618	Include ".....assessment (see section 3.4.3). Another possibility, although technically more complicated, is the use of cardiac pacing in conscious animals."
16, 636	3.4.1.4. Influence of Heart Rate Change on the QT interval. We applaud the authors for raising the point that Bazzett or Federicia calculations can produce misleading results when large differences in heart rate are evident.
16, 637	Change the sentence to "The QT interval and heart rate have an inverse, non-linear relationship, which can vary among species, between animals, or even within the same animal at different occasions (e.g. due to differences in autonomic tone).
17, 650	Include "...can yield misleading data, especially this is true for Bazett when ...."
17, 656-658	Please rewrite more succinctly, e.g. "In vitro and in vivo studies including other ECG and cardiac parameters can be helpful in interpreting complex dose-response relationships"
18, 708	Spelling of "oximeter".
19, 762	Include "....effects on repolarization. However, a potential drawback of using ERP is the risk for false positives, i.e. compounds that delay refractoriness by mechanisms that are unrelated to repolarization (e.g. sodium channel block)."